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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/606,129	06/28/2000	Mahin D. Maines	176/60792(6-11415-868)	5529

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	12

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,129	MAINES, MAHIN D.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 68-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 68-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-9, 68-76 are pending.

Applicant's amendment of claims 1 and 4, cancellation of claims 10-67, and addition of claims 68-76 in Paper No. 11, filed on 8/23/2002 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/141309 filed on 6/28/1999 and 60/163223 filed on 11/3/1999.

Drawings

2. The formal drawings submitted on 8/23/2002 have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-9 and 68-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 1 and 68 (claims 2-9, 69-76 dependent thereon) are indefinite in the recitation of "active fragment or variant thereof" for the following reasons. First, the claim is unclear absent a statement defining which activity is being referred to. A polypeptide fragment can be "active" if it is able to induce an immune response which would result in the production of antibodies. Second, it is unclear what the meaning of the term variant is within the context of the claim since in the absent of a definition, a variant can be anything that deviates from the original polypeptide. It is suggested that the claim be amended to recite instead "fragment with kinase regulatory activity". For examination purposes, it will be assumed that the term "active" refers to kinase regulatory activity and the term "variant" will be interpreted as "any polypeptide". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9, 68-70, 74-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 7-9, and 74-76 are directed to a method of regulating the activity of a genus of protein kinases with a genus of biliverdin reductases. Claims 2-3, 68-70 are directed to a method of regulating the activity of protein kinase A or C with a genus of biliverdin reductases. Claims

4-6 are directed to a method of regulating the activity of a genus of protein kinases with rat or human biliverdin reductases. While the specification discloses the structure and function of a rat biliverdin reductase of SEQ ID NO: 4 and fragments thereof (SEQ ID NO: 18 and 19) as well as the structure and function of the human biliverdin reductases of SEQ ID NO: 1, 3 and fragments thereof (SEQ ID NO: 34 and 35), there is no disclosure of other biliverdin reductases from other sources. No information as to the critical structural elements a polypeptide should have to display biliverdin reductase activity has been provided either. Furthermore, the specification fails to adequately describe the claimed method since it only discloses the regulation of one protein kinase (protein kinase C) with biliverdin reductase. This is not sufficient since not all protein kinases are expected to be phosphorylated and/or regulated by biliverdin reductase.

While one could argue that the disclosure of a rat and human biliverdin reductase is sufficient to adequately describe the genus of biliverdin reductases of the claimed method since one can isolate other biliverdin reductases by sequence comparison, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork (Genome Research, 10:348-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998)

teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a few species of the genus which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus required to practice the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

8. Claim 1 was rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. This rejection was explained in detail in Paper No. 10, mailed on 3/20/2002.

10. Applicants argue that the amendment to the claim, which now recites the limitation "active", is sufficient to overcome the rejection. In addition, Applicants assert that the specification provides several functional domains of biliverdin reductase and the regulation of protein kinase C with the biliverdin reductases of the instant application, therefore, one of skill in the art can identify other kinases which are regulated by biliverdin reductases or fragments or variants.

11. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The term "active" as amended does not clearly state which activity must be present in the fragment or variant thereof as explained above. See rejection under 35

USC §112, second paragraph. While amending the claim as suggested would obviate one of the basis of rejection, the specification fails to adequately describe the claimed method since there is no teaching or suggestion as to which protein kinases can be regulated with biliverdin reductase other than protein kinase C, nor there is sufficient description of the genus of biliverdin reductases required to practice the claimed method. See reasons discussed above. The specification, while disclosing several functional domains in the polypeptide of SEQ ID NO: 1 (human biliverdin reductase), does not disclose which of those several domains are essential to display the kinase regulatory activity desired. The sequence homology example (page 16) provided shows that only a few of the domains in the polypeptide of SEQ ID NO: 1 are present in the polypeptide of SEQ ID NO: 3, however there is no indication as to whether the common domains found in the polypeptide of SEQ ID NO: 3 are indicative of biliverdin reductase activity. Therefore, for the reasons discussed above, one of skill in the art cannot reasonably conclude that Applicant was in possession of the claimed invention at the time the application was filed.

12. Claims 1-9, 68-70, 74-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for regulating the activity of human protein kinase C with the human biliverdin reductase of SEQ ID NO: 1 or 3 or the peptides of SEQ ID NO: 18, 19, 34 or 35, does not reasonably provide enablement for a method for regulating the activity of any protein kinase with any biliverdin reductase, active fragment or variant thereof. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims is not commensurate with the enablement provided in regard to the large number of unknown biliverdin reductase polypeptides required to practice the claimed method and the unknown protein kinases which can be regulated with the claimed method. As indicated previously, the specification discloses the structure and function of the polypeptides of SEQ ID NO: 1, 3, 4, 18, 19, 34 and 35. The state of the art teaches that the isolation of other polypeptides of similar function is unpredictable based on sequence homology. See the teachings of Bork (Genome Research, 10:348-400, 2000), Broun et al. (Science 282:1315-1317, 1998), Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) already discussed. Since the amino acid sequence determines the function of a polypeptide, one would require some knowledge and/or guidance as to how structure relates to function to isolate biliverdin reductase polypeptides with kinase regulating activity in order to practice the claimed method. In addition, as discussed above, it is not expected that all protein kinases will be regulated by all biliverdin reductases. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability

of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those polypeptides, as encompassed by the claim, with biliverdin reductase activity, to practice the claimed method as well as which protein kinases can be regulated with said method. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

13. This rejection was applied to claims 1-5 and 7-9 in previous Office Action Paper No. 10, mailed on 3/20/2002.

14. Applicants argue that a declaration by inventor Mahin D. Maines under 37 CFR 1.132, which reports her findings in regard to the possible regulation of the Goodpasture Antigen Binding Protein (GABP) by biliverdin reductase, is sufficient for supporting the argument that other proteins can be regulated by biliverdin reductase besides protein kinase C. In addition, Applicants argue that the Examiner misinterpreted the teachings of Salim et al. (J. Biol. Chem. 276(14):10929-10934, 2001) since the reference does not teach that biliverdin reductase is not a tyrosine phosphoprotein. Furthermore, Applicants argue that the specification clearly teaches that biliverdin reductase is a serine/threonine/tyrosine phosphoprotein, therefore biliverdin reductase will regulate the activity of serine/threonine kinases as well as tyrosine kinases.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The evidence presented by the declaration of inventor Mahin Maines teaches that GABP may be regulated by biliverdin reductase but does not provide support to the argument that any protein kinase is regulated by biliverdin reductase, as encompassed by the

claims. In regard to the teachings of Salim et al. and the instant application with respect to the characterization of biliverdin reductase as a tyrosine phosphoprotein, even if biliverdin reductase is a serine/threonine/tyrosine phosphoprotein as asserted, it is not expected that all protein kinases (serine/threonine and tyrosine kinases) will be regulated by biliverdin reductases due to the fact that kinases are part of a large family of enzymes with different characteristics, substrates, specificities and function. Without any teaching or suggestion as to which serine/threonine or tyrosine kinases can be regulated by biliverdin reductase or which critical structural elements should be present in a kinase to be regulated by biliverdin reductase, one of skill in the art would have to go through the burden of undue experimentation to practice the full scope of the claimed method. Thus Applicant has not provided sufficient guidance to enable one of skill in the art to use the invention in a manner reasonably correlated with the scope of the claims.

16. Claim 8 was rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

17. This rejection was discussed in detail in Paper No. 10, mailed on 3/20/2002.

18. Applicants argue that the specification describes techniques to deliver biliverdin reductase to patients via liposome delivery, conjugates and chimera. Furthermore, Applicants argue that the administration of biliverdin reductase can be performed for regulation of protein kinase C activity. Since the specification teaches that biliverdin reductase is a

serine/threonine/tyrosine phosphoprotein and the evidence presented in the declaration by inventor Mahin Maines indicated the binding of biliverdin reductase to GABP, Applicants conclude that one of skill in the art can expect biliverdin reductase to regulate the activity of other kinases. Consequently, the present specification provides sufficient description of the claimed invention.

19. Applicant's arguments in regard to the description of techniques to deliver biliverdin reductase and the assertion that biliverdin reductase can be administered for regulation of protein kinase C activity in the specification, are deemed persuasive to overcome the instant rejection. Therefore, this rejection is hereby withdrawn.

20. Claims 1-8 and 69-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for regulating the activity of human protein kinase C with the human biliverdin reductase of SEQ ID NO: 1 or 3 or the peptides of SEQ ID NO: 18, 19, 34 or 35 in vitro, does not reasonably provide enablement for such method in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

21. This rejection was discussed in previous Office Action Paper No. 10, mailed on 3/20/2002, and is applied to claims 1-7 and newly added claim 69-75 for the reasons of record.

22. Applicants argue that in vivo data is not a requirement under 35 USC and since Applicants have demonstrated the interaction between biliverdin reductase and protein kinase C as well as GABP (evidence shown in declaration), there is no reason to doubt that biliverdin

reductase can regulate protein kinases in vivo. Applicants also provided additional references by Hara et al. (J. Cereb. Blood Flow Metab. 10:646-653, 1990) and Meyer et al. (Int. J. Cancer 43:851-85, 1989) to further support the argument that since in vivo delivery of inhibitors of protein kinase C has been used successfully in the regulation of protein kinase C activity in vivo, the results of the present application are predictive of in vivo success.

23. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. While it is agreed that in vivo data is not an absolute requirement of 35 USC for enablement, one of skill in the art would still require some knowledge or guidance as to how to practice the full scope of the claimed invention in vivo. In the instant case, there is no evidence in the specification or the state of the art as to whether biliverdin reductase can in fact regulate kinase activity in vivo or even which protein kinases can be regulated in vivo. The only information provided is that human/rat biliverdin reductase and/or certain fragments thereof may regulate human protein kinase C in vitro. Those of skill in the art recognize that in vitro assays, which are carried out in very narrowly defined and controlled conditions, are useful to observe basic physiological and cellular phenomenon, however they cannot be used to extrapolate in vivo results due to the increased complexity and cell-cell interaction of the in vivo environment. Since kinases in vivo are usually part of very complex networks of signaling pathways, their activity is highly regulated by the numerous interactions among different cells and interactions between the cell and the outside environment. Therefore, one of skill in the art cannot reasonably expect that in vitro results can be extrapolated in vivo. While the references presented show that staurosporine (and derivatives) can inhibit protein kinase C activity in vivo, neither the references, the state of the art or the specification have provided sufficient evidence

such that one of skill in the art can reasonably expect biliverdin reductase to regulate protein kinase C activity or any protein kinase in vivo, as encompassed by the claims.

Double Patenting

24. Applicant is advised that should claims 7-9 be found allowable, claims 74-76 will be objected to under 37 CFR 1.75 as being a duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). It is suggested that claim 74 be amended to depend upon claim 68.

Conclusion

25. No claim is in condition for allowance.

26. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

27. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE

COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 14, 2002

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